

Articles

A Gentamicin Order Form Improves Its Use

KETSY SMITH, BS (PHARM), and JOSEPH P. RINDONE, PHARM.D, Prescott, Arizona

To assess the effects of implementing a standardized order form on the prescribing and monitoring of gentamicin sulfate at a nonteaching Veterans Affairs Medical Center, we prospectively evaluated the prescribing and monitoring of gentamicin for 14 months after the use of such a form was implemented. The data collected included dosing, initial serum gentamicin concentrations, and serum creatinine measurements. These data were compared with similar data obtained during a period of 6 months before the order form was used. A total of 76 patient records were reviewed, 39 before the use of the order form and 47 after the order form was implemented. Gentamicin peak concentrations were statistically higher in the group treated after the order form was implemented. No differences were seen in gentamicin trough concentrations. The timely measurement of serum gentamicin concentrations and serum creatinine levels was improved in the group for whom the order form was used. The order form was completed satisfactorily in 44 patients (94%). We conclude that implementing a standardized order form improved the use of gentamicin.

(Smith K, Rindone JP. A gentamicin order form improves its use. *West J Med* 1998; 168:494-498)

Gentamicin sulfate remains an important antibiotic in the treatment of gram-negative infections. The drug is most effective when particular attention is paid to proper dosing and monitoring of both serum concentrations and renal function. Numerous reports, however, have demonstrated that physicians do not use the proper doses and do not properly monitor the use of gentamicin and other aminoglycosides.¹⁻³ This has led, in part, to the development of pharmacokinetic dosing services that have improved the use of gentamicin, with improved patient outcomes.^{4,5} Unfortunately, resources for specialized dosing services are not always available or accepted by all physicians. These problems were encountered at the Veterans Affairs Medical Center, Prescott, Arizona. In response to a medication use evaluation that demonstrated an inappropriate use of gentamicin, it was decided to implement a physician-initiated standardized order form for prescribing gentamicin. This order form integrates a simple dosing table into a concise, step-by-step approach to the dosing and monitoring of gentamicin.

Methods

The gentamicin order form (Figure 1) was implemented in November 1995. It was developed by pharmacy staff and approved by the medical staff and the Pharmacy and Therapeutics Committee. All calculations specified on

the form were performed by physicians ordering the drug, but were checked by a pharmacist before the drug was prepared and dispensed. Creatinine clearance was estimated using the Cockcroft and Gault formula, as shown in Figure 1. The creatinine clearance was multiplied by 0.85 for women. The total weight of the patient was used to calculate the loading dose and creatinine clearance. Maintenance doses were calculated as a percentage of the loading dose as specified in the dosing table and administered at set times. The minimum dosing interval was set at 12 and 24 hours. Serum concentrations were measured two days after the loading dose to assure that steady-state conditions were reached in most cases. Blood specimens for trough serum concentrations were drawn immediately before and for peak serum concentrations 30 minutes after the 30-minute infusion was completed. All subsequent serum concentrations were monitored by a pharmacist, and dosing changes were suggested to the physician when a dosage correction was needed. Serum creatinine levels were measured every other day or more frequently as needed.

The order form was mandated for use in all patients receiving gentamicin, with the possible exception of patients prescribed gentamicin for suspected lower urinary tract infections or for prophylaxis. The order form was also used for the administration of tobramycin, but this agent is nonformulary and is seldom used. Before the order form was implemented, the 16 physicians, 3 physi-

Figure 1.—The standardized order form for prescribing gentamicin sulfate at the Veterans Affairs Medical Center, Prescott, Arizona, is shown.

1. Baseline serum creatinine level now.
2. Patient's total body weight _____ kg
3. Calculate creatinine clearance:

$$\frac{(140 - \text{age}) (\text{weight in kg})}{\text{serum creatinine} \times 72} = \text{creatinine clearance}$$
 multiply creatinine clearance $\times 0.85$ for women
4. Loading dose (2 mg/kg) = _____ mg, give now
5. Maintenance dose based on percentage of loading dose using the following table:

Creatinine Clearance, ml/min	Percentage of Loading Dose every 12 hr	Percentage of Loading Dose every 24 hr
>80	100	—
60-80	85	—
40-59	—	100
20-39	—	80
<20	Call pharmacy for consultation	

Maintenance dose = _____

6. Draw trough level immediately before and a peak level 30 minutes after infusion around the 0900-hr dose 2 days after the loading dose.
7. Serum creatinine level every other day.
8. Pharmacy consultation for follow-up dosing.

cians' assistants, and 4 nurse practitioners employed by the medical center were taught how to use it.

After implementation of the order form, data on all patients receiving gentamicin were prospectively collected for 14 months. These data included patient demographics, initial peak and trough serum concentrations, monitoring of serum creatinine levels, and accuracy in completing the form. These data were compared with similar data that were retrospectively collected during a six-month period before the order form was implemented. All data, both retrospective and prospective, were collected using patient-specific pharmacy and laboratory computer records. For groups—patients before and those after the order form was implemented—when blood specimens for trough concentrations were drawn early and those for peak concentrations drawn late, the expected peak and trough serum concentrations were calculated using standard pharmacokinetic formulas.

Data were analyzed by using an unpaired *t* test when comparing means and a *z* test when comparing proportions. Statistical significance was set at an α of .05.

Results

The medical records of 76 patients were reviewed: 39 patients before the order form was implemented and 47 patients after it was implemented. There were no statistically significant differences between groups in demographics or clinical variables (Table 1).

The mean peak serum concentration was significantly higher in the patients for whom the order form was used (Table 2). Forty-three of these patients (91%) had initial peak serum concentrations greater than 5 μg per ml com-

pared with 17 (44%) of the group before the use of the order form ($P < .001$). Twenty patients (42%) for whom the order form was used had peak concentrations greater than 8 μg per ml (Figure 2). There was no difference in mean trough concentrations between the groups. Forty-three patients (91%) for whom the order form was used received an appropriate loading dose compared with none in the group before the order form was implemented. There was a trend toward higher daily doses in the patients with the order form that did not reach statistical significance. Peak and trough concentrations as well as serum creatinine levels were significantly more likely to be measured in the patients for whom the order form was used. Calculations performed while using the order form were accurate in all but three patients. In one of those patients, the weight in pounds was not converted to kilograms; in another, an arithmetic error was made in calculating the serum creatinine level; and in the third patient, the dosing table was bypassed completely.

TABLE 1.—Clinical and Demographic Variables in Patients Administered Gentamicin Sulfate*

Variable	No Protocol (n=39)	Protocol (n=47)
Age, yr	.71 \pm 10	69 \pm 12
Weight, kg	.79 \pm 24	75 \pm 17
Baseline serum creatinine, mmol/liter	.106 \pm 35	114 \pm 70
Calculated creatinine clearance, ml/min	.69 \pm 34	70 \pm 29

*Data are given as the mean \pm SD.

TABLE 2.—Gentamicin Serum Concentrations and Monitoring Variables

Variable	No Protocol	Protocol	P Value
Peak serum level, $\mu\text{g/ml}$ *	4.8 ± 1.9	7.8 ± 2.7	<.001
Trough serum level, $\mu\text{g/ml}$ *	1.1 ± 0.9	1.1 ± 0.7	.86
Daily dose, mg*	182 ± 49	215 ± 96	.06
Patients with peak level $>5 \mu\text{g/ml}$ †	17 (44)	43 (91)	<.001
Patients with trough level $>2 \mu\text{g/ml}$ †	4 (10)	5 (11)	.72
Patients with 2 mg/kg loading dose†	0 (0)	43 (91)	<.001
Patients with levels measured within 48 hr of loading dose†	22 (56)	45 (96)	<.001
Patients with serum creatinine checked at least every other day†	28 (72)	45 (96)	.001

*Data are given as the mean \pm SD.

†Data are given as the number of patients, with percentage given in parentheses.

Discussion

These results show that the use of a standardized order form for prescribing gentamicin, primarily implemented by physicians, greatly improved the use of this drug. Not only were peak serum concentrations higher in the group for whom the order form was used, but the timely measuring of serum concentrations and serum creatinine levels was significantly improved.

The goal of the dosing table was to achieve a peak concentration of at least $5 \mu\text{g}$ per ml and a trough concentration of less than $2 \mu\text{g}$ per ml. These concentrations were selected based on data that demonstrated improved patient outcome and a decreased incidence of nephrotoxicity when these concentrations are attained.⁶⁻⁸ This dosing method was patterned after that of Hull and Sarubbi⁹ but was modified and simplified to specify higher doses administered less frequently to achieve higher peak and lower trough concentrations. The original Hull and Sarubbi nomogram emphasized administering a smaller fraction of the loading dose every eight hours. One study has shown that this method often results in low peak and

high trough serum concentrations.¹⁰ Assuming a normal volume of distribution (0.25 liters per kg) and a serum half-life of two to three hours in patients with normal renal function,¹¹ a dose of gentamicin of 2 mg per kg should result in peak concentrations ranging from 5 to 8 μg per ml, with resultant trough concentrations of less than $2 \mu\text{g}$ per ml when the dose is given every 12 to 24 hours. This is what we observed in most of the patients for whom the order form was used. Even though this dosing method was not specifically designed to achieve high peak concentrations ($>8 \mu\text{g}$ per ml, for example), this was accomplished in 19 of 47 patients. In the pre-order-form patients, 12 (32%) of the patients were given a dose every 8 hours (Figure 3), which could account, in part, for the low peak serum concentrations that occurred.

Another method of giving aminoglycosides is to administer a large dose once a day. Higher peak concentrations will produce a higher ratio of peak concentration to minimal inhibitory concentration, which has been associated with an improved outcome.¹² Meta-analysis has shown, however, that a dose of 4 to 6.6 mg

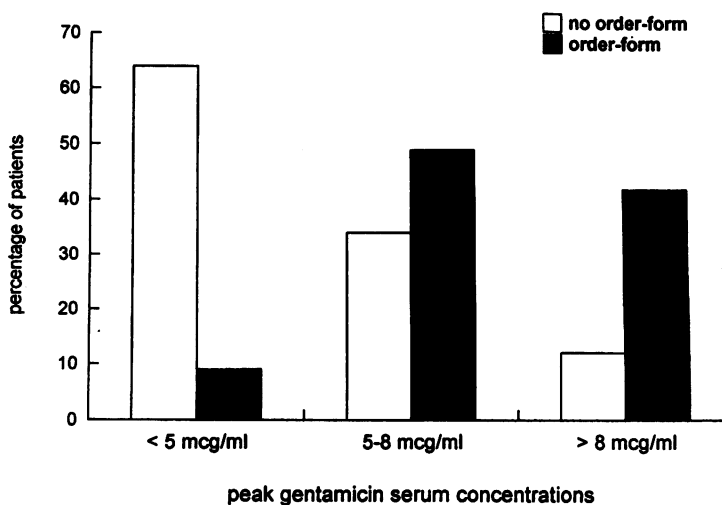


Figure 2.—The distribution of initial peak gentamicin serum concentrations is shown.

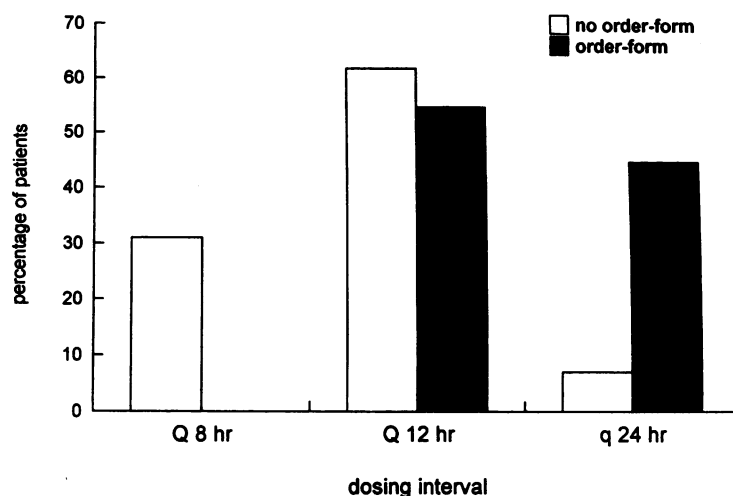


Figure 3.—The distribution of dosing intervals is shown.

per kg of either gentamicin or netilmicin sulfate does not have superior efficacy to standard doses administered every eight hours.^{13,14} Despite potential theoretical and practical advantages, once-a-day dosing has not been universally accepted.^{15,16} Unresolved issues such as its use in patients with renal impairment, therapy without concomitant β -lactam antibiotics, the treatment of endocarditis, and use in immunocompromised patients or in elderly patients limits its application. For patients with impaired renal function, some authors recommend that the once-a-day dosing method be changed to every 36 or 48 hours to ensure that trough serum concentrations remain below 2 μ g per ml.¹⁷ Although easy to administer, these nonroutine administration intervals cause confusion, which may lead to errors in administration and interfere with the timely measurement of serum concentrations.

It is possible that our method of administering gentamicin may not result in similar serum concentrations in other patient groups. The patients in the study were largely older men without serious renal impairment. Most of these patients were hospital patients and not considered critically ill. Studies have shown that the volume of distribution of gentamicin is considerably higher in young patients, patients with edema, and patients who are critically ill.^{11,18} Administering a conventional dose of 2 mg per kg may not achieve adequate peak concentrations in these patients.¹⁹ Some authors recommend higher loading doses in a patient who is seriously ill.²⁰ Further study with this dosing regimen in younger or sicker patients would help clarify this issue.

A possible criticism of this dosing method is that patients' ideal body weight was not used in the dosage calculation. This was not included in the order form for two reasons. First, the volume of distribution and clearance of aminoglycosides are higher in morbidly obese patients.²¹ In these patients, higher doses are required to achieve comparable serum concentrations than in patients who have a similarly calculated ideal body weight. Our

concern is that underdosing may occur if "ideal body weight" was uniformly used. Second, to make the order form simple and uncomplicated, we omitted the published formulas for estimating ideal body weights for both moderately and morbidly obese patients.¹¹

Conclusion

In patients who are chronically ill, elderly, or male, the use of a simplified dosing method for administering gentamicin using a physician-initiated order form resulted in higher peak serum concentrations in most patients. In addition, the proper timing of serum concentration determinations and consistent measurement of serum creatinine levels were significantly enhanced.

REFERENCES

1. Anderson AC, Hodges GR, Barnes WG. Determination of serum gentamicin sulfate levels: ordering patterns and use as a guide to therapy. *Arch Intern Med* 1976; 136:785-787
2. Flynn TW, Pevonka MP, Stewart RB, Weber CE, Yost RL. Use of serum gentamicin levels in hospitalized patients. *Am J Hosp Pharm* 1978; 35:806-808
3. Haslett TM, Reynolds JR. Aminoglycoside utilization study. *Hosp Pharm* 1988; 23:872-880
4. Crist KD, Nahata MC, Ety J. Positive impact of a therapeutic drug-monitoring program on total aminoglycoside dose and cost of hospitalization. *Ther Drug Monit* 1987; 9:306-310
5. Sveska KJ, Rogge BD, Solomon DK, Hoffmann RP. Outcome of patients treated by an aminoglycoside pharmacokinetic dosing service. *Am J Hosp Pharm* 1985; 43:2472-2478
6. Moore RD, Smith CR, Lietmann PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am J Med* 1984; 77:657-662
7. Moore RD, Smith CR, Lietmann PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J Infect Dis* 1984; 149:443-448
8. Noone P, Parsons TMC, Patison JR, Slack RCB, Garfield-Davies D, Hughes K. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. *Br Med J* 1974; 1:477-481
9. Hull JH, Sarubbi FA. Gentamicin serum concentrations: pharmacokinetic predictions. *Ann Intern Med* 1976; 85:183-189
10. Lesar TS, Rotschafer JC, Strand LM, Solem LD, Zaske DE. Gentamicin dosing errors with four commonly used nomograms. *JAMA* 1982; 248:1190-1193
11. Winter ME. Aminoglycoside antibiotics. chap 1. *Basic Clinical Pharmacokinetics*. Vancouver, WA: Applied Therapeutics; 1994, pp 128-176
12. Moore RD, Lietmann PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory con-

centration. *J Infect Dis* 1987; 155:93–99

13. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med* 1996; 124:717–725

14. Ferriols-Lisart R, Alos-Almina M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health-Syst Pharm* 1996; 53:1141–1150

15. Rotschafer JC, Rybak MJ. Single daily dosing of aminoglycosides: a commentary. *Ann Pharmacother* 1994; 28:797–801

16. Levison ME. New dosing regimens for aminoglycoside antibiotics. *Ann Intern Med* 1992; 117:693–694

17. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to

2,184 adult patients. *Antimicrob Agents Chemother* 1995; 39:650–655

18. Dasta JF, Armstrong DK. Variability in aminoglycoside pharmacokinetics in critically ill surgical patients. *Crit Care Med* 1988; 16:327–330

19. Summer WR, Michael JR, Lipsky JJ. Initial aminoglycoside levels in the critically ill. *Crit Care Med* 1983; 11:948–950

20. Chelluri L, Warren J, Jastremski MS. Pharmacokinetics of a 3 mg/kg body weight loading dose of gentamicin or tobramycin in critically ill patients. *Chest* 1989; 95:1295–1297

21. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur J Clin Pharmacol* 1983; 24:643–647